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08/653,294	05/24/1996	CAROL CLAYBERGER	286002020023	5995

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HL

Office Action Summary	Application No.	Applicant(s)	
	08/653,294	CLAYBERGER ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *28-34 and 36-38* is/are allowed.

6)☐ Claim(s) *35,39 and 41* is/are rejected.

7)☐ Claim(s) *40* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 12/3/04 is acknowledged and has been entered.

2. Claims 28-41 are presently being examined.

3. The terminal disclaimer filed on 12/3/04 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,436,903 B1 has been reviewed and is accepted. The terminal disclaimer has been recorded.

4. The terminal disclaimer filed on 12/3/04 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 5,723,128 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The following are new grounds of rejection necessitated by Applicant's amendment filed 12/3/04.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claim 41 is rejected under 103(a) as being unpatentable over WO 88/05784 in view of Wong et al (Human Immunology 1992, 35/3, 200-208), U.S. Patent No. 5,073,540 and U.S. Patent No. 5,478,925.

WO 88/05784 teaches peptides which are cross reactive with portions of the $\alpha 1$ or α 2 domains of MHC class I, with the sequence of those of the instant claims (especially claim 1 and abstract). WO 88/05784 also teaches modification of such peptides using conventional techniques to extend their biological half lives (especially pages 21-23). Page 10 of the instant application discloses such conventional techniques.

WO 88/05784 explicitly teaches use of such peptides for prolonging graft survival time by reducing rejection caused by CTL. WO 88/05784 teaches using the said peptides linked to other peptides or proteins of interest.

WO 88/05784 does not teach dimerization of the peptides.

Wong et al teaches foci of TCR receptor aggregation upon binding to MHC class I molecules.

Patent No. 5,073,540 discloses peptides useful as antagonists or agonists for membrane receptors, one portion comprising the same structure as the peptides of the instant application (especially columns 7 and 8). Patent No. 5,073,540 further discloses that oligopeptides may be employed that are capable of mimicking the site of the Class I antigen associated with binding to the receptor, thus substituting for the class I antigen (especially paragraph spanning columns 4 and 5).

U.S. Patent No. 5,478,925 discloses receptors that exist in aggregated form when exposed to ligand. U.S. Patent No. 5,478,925 further discloses binding proteins that are identical to the extra-cellular domains of the said receptors that compete for binding and that the monomers must be administered in very high doses in order to result in effective inhibition of binding when administered to humans. U.S. Patent No. 5,478,925 discloses that multimers of the proteins are more effective in inhibiting activity at lower doses, since they can effectively compete for binding sites on the aggregates of the cell surface receptors. (especially columns 1, 2 and 3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the prior art peptides taught by WO 88/05784 as multimers, i.e., at least dimers, as is taught by U.S. Patent No. 5,478,925 for other receptor mimicking and inhibiting polypeptides, and to test functional activity on surface receptors or lymphocyte activity of the modified peptides using the assays taught by WO 88/05784 (especially page 25), and to use the said multimeric peptides in the method of inhibiting graft rejection taught by WO 88/05784 for prolonging graft survival time by reducing rejection caused by CTL which comprise TCR that aggregate upon binding to MHC class I molecules as taught by Wong et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to stimulate or inhibit membrane receptors as taught by WO 88/05784 and as disclosed by Patent No. 5,073,540 and/or to prolong graft survival time as taught by WO 88/05784 because Wong et al teaches that TCR on CTL aggregate upon binding class I MHC and U.S. Patent No. 5,478,925 discloses that multimers are more effective in inhibiting activity at lower doses since they can effectively compete for binding sites on the aggregates of cell surface receptors and because one of ordinary skill in the art at the time the invention was made would have expected the dimers of the same unit to exert the same functional effects as a monomer.

Applicant's arguments in Applicant's amendment filed 12/3/04 have been fully considered but are not persuasive.

Applicant's position in the said amendment beginning on page 5 and continuing on to page 7 are of record. Briefly, Applicant's position is: (1) that the dimeric peptides are superior in their ability to completely inhibit cytolysis and inhibit T cell proliferation, and Applicant cites the specification at page 22, lines 1-9 and page 24, lines 15-19, and asserts that the monomeric peptide lacks the ability to completely inhibit cytolysis as well as having no effect on

proliferation and that the Examiner has assumed that the distinct features of complete inhibition of cytoxicity and inhibition of proliferation not observed with the monomeric peptide are simply attributable to increased half life or interference with TCR aggregation. (2) That the four hour assay in the specification does not address issues relating to half life. (3) That other MHC derived peptides are known to have modulatory activities that are distinct from interfering with MHC/TCR aggregation, and Applicant cites US Patent No. 5,935,797 and Exhibits A and B (i.e., Nobner et al and Ling et al). (4) That these said cites are objective evidence that a person of skill in the art would not rely on the theory of TCR aggregation inhibition as motivation to combine Krensky with the other cited references because these peptides can mediate their effects in any number of ways that may or may not be increased if dimeric peptides are employed.

It is the Examiner's position that: (1 and 2) The specification at lines 1-9 on page 22 discloses that the alpha-alpha dimer peptide HLA-B2702.75-84/75-84 RENLRIALRYRENLRIALRY, was able to inhibit lysis by CTL comparably to that of the beta-alpha dimer YRLAIRLNERRENLRIALRY, and comparably to the HLA-B2702.60-84 peptide (a longer peptide with non-identical amino acid residues at positions 60-74 (not identical with peptide 75-84 or 84-75) and with amino acid residues 75-85 identical), i.e., approximately 5-fold more. It is the Examiner's further position that the HLA-B2702.60-84 peptide contains the HLA-B2702.75-84 monomer peptide in a position carboxy terminal to unrelated amino acid sequence in a longer peptide about the same length as the dimer peptides, and it has superior abilities commensurate with the alpha-alpha dimer peptide HLA-B2702.75-84/75-84 RENLRIALRYRENLRIALRY and the beta-alpha dimer YRLAIRLNERRENLRIALRY, indicating that either length, protection from amino terminal proteases or the non-related amino terminal sequence itself is important for functionality (of the RENLRIALRY sequence) in the HLA-B2702.60-84 peptide. The specification at lines 15-19 on page 24 discloses that in a proliferation assay using immobilized anti-CD3 antibody to stimulate purified T cells, the beta-alpha dimer HLA-B2702.84-75/75-84 could inhibit T cell proliferation, whereas the HLA-B2702.75-84, i.e., RENLRIALRY, and the HLAB7.75-84, i.e., RESLRNLRGY, peptides could not. It is the Examiner's position that Table 3 of the specification appears to indicate that the HLA-B2702.75-84 monomer can inhibit T cell proliferation mediated by stimulation with Con A, that the specification at the results section on page 28- page 30 indicates that both the HLA-B2702.75-84 and the HLA-B7.75-84 peptides could block differentiation of rat spelenocytes into allospecific CTL in vivo and in vitro and when injected into rats, resulted in splenocytes that were not responsive to allogenic challenge, and that intravenous administration of these B2702.75-84 and the HLA-B7.75-84 monomer peptides plus a short course of CsA could tolerize in mice or rats, respectively, to increase graft survival (pages 31-35 of the specification). In addition, when HLA-B2702.75-84 was converted to a peptide with all D-amino acid residues, i.e., converted to residues resistant to proteolysis, the graft survival period was extended. It is the Examiner's position that functionality was observed with the monomer peptides. (3 and 4) It is the Examiner's position that with regard to Applicant's arguments to the Exhibits Nobner et al and Ling et al, that identification of binding of the B2702.75-84 (or dimeric) peptide to HSP 70 due to possession of a motif for peptides that bind

to HSP 70 (i.e., hydrophobic or aromatic amino acid residues at relative positions 2, 4 and 6, and positively charged amino acid residues at non-anchor positions) in the instance of Nobner et al, or the identification of two proteins BiP (a HSP 70 family member protein) and VCAM-1 that bind to B2702.75-84 from a yeast two-hybrid screening assay in the instance of Ling et al, in the absence of evidence that binding to any or all of these proteins mediates a function, is not evidence that B2702.75-84 mediates function through binding to these molecules, and hence does not obviate the motivation to combine references in the instant rejection. In addition, both said Exhibit references have publication dates that are after the effective filing date of the instant application. The disclosure of U.S. Patent No. 5,935,797 is to MHC class II peptides and the effective filing date of '797 is post effective filing date of the instant application.

It is the Examiner's further position that the Examiner's arguments of record in the previous Office Action mailed 7/7/04 apply herein.

7. Claim 41 is rejected under 103(a) as being unpatentable over WO 88/05784 in view of U.S. Patent No. 6,419,931.

WO 88/05784 teaches peptides which are cross reactive with portions of the $\alpha 1$ or α 2 domains of MHC class I, with the sequence of those of the instant claims (especially claim 1 and abstract). WO 88/05784 also teaches modification of such peptides using conventional techniques to extend their biological half lives (especially pages 21-23). Page 10 of the instant application discloses such conventional techniques. WO 88/05784 explicitly teaches use of such peptides for prolonging graft survival time by reducing rejection caused by CTL. WO 88/05784 teaches using the said peptides linked to other peptides or proteins of interest.

WO 88/05784 does not teach dimerization of the peptides.

U.S. Patent No. 6,419,931 discloses that peptides that modulate CTL can be combined to form multimers and that the same peptide can be linked to itself to form a homopolymer, i.e., a dimer (especially column 17 at lines 4-38-43).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the prior art peptides taught by WO 88/05784 as dimers as disclosed by taught by U.S. Patent No. 6,419,931, and to test functional activity on surface receptors or lymphocyte activity of the modified peptides using the assays taught by WO 88/05784 (especially page 25), and to use the said multimeric peptides in the method of inhibiting graft rejection taught by WO 88/05784 for prolonging graft survival time.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to stimulate or inhibit membrane receptors as taught by WO 88/05784 and to prolong graft survival time as taught by WO 88/05784 because U.S. Patent No. 6,419,931 discloses that peptides that modulate CTL can be combined to form multimers and that the same peptide can be linked to itself to form a homopolymer, i.e., a dimer, and one of ordinary skill in the art at the time the invention was made would have expected the dimers of the same unit to exert at least the same functional effects as a monomer.

Applicant's arguments in Applicant's amendment filed 12/3/04 have been fully considered but are not persuasive for the reasons of record and as enunciated at item #6 of this Action.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 39 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed peptide dimer that *consists essentially of* the SEQ ID NO recited in the instant claim.

The instant claim encompasses a peptide dimer that consists essentially of the SEQ ID NO recited in the instant claims. The said peptide dimer can comprise amino acid residues that flank the said sequences in the protein of origin, or can be any number of undisclosed and unrelated sequences, or may contain modification in the form of additions, deletions, or substitutions to the core defined amino acid sequence. There is insufficient disclosure in the specification on peptides of unlimited length and/or modifications consisting essentially of one of the sequences recited in the instant claim.

The specification discloses that "For the most part, the peptides will be based on a 6 amino acid sequence found at positions 79-84 in the HLA-B [α1-domain] sequence, but may include amino acids related to those at HLA-B positions 60-84 [the B2702.60-84 peptide is disclosed in the instant specification], as well as additional irrelevant sequences", that they are CTL immunomodulating compositions and as such must be shown to inhibit CTL-mediated lysis in

cytotoxicity assays and/or inhibit anti-CD3-induced proliferation of purified T cells (page 4 at lines 15-24 and page 6 at lines 3-6).
The specification does not disclose any peptides comprising the sequences recited in the instant claims wherein the flanking amino acid residues are not from HLA-B positions 60-84, nor wherein amino acid residues are deleted, or added or modified within the core defined sequence of amino acid residues 75-84, other than a few specific substitutions at a few specific positions.

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. However, a generic statement such as a peptide dimer that "consists essentially of" one of the recited SEQ ID NO that "inhibits CTL-mediated cytotoxicity", is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by the property of containing one of the recited sequences, or an undisclosed modified sequence. It does not specifically define the compounds that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others, other than that they comprise one of the recited sequences. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

One of ordinary skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

10. Claim 39 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

The specification does not disclose how make and or/use an isolated peptide dimer that inhibits CTL-mediated cytotoxicity and *consists essentially of* one of the sequences in the instant claim.

The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass a peptide dimer consisting essentially of one of the sequences recited in the instant claims capable of inhibiting CTL-mediated cytotoxicity. The said peptide dimer/composition thereof can comprise amino acid residues that flank the said sequences in the protein of origin, or can be any number of undisclosed and unrelated

sequences, and in addition, the amino acid residues of the SEQ ID NO may also be substituted or altered or deleted or additions may be made to the said amino acid residues of the SEQ ID NO.

The specification discloses "For the most part, the peptides will be based on a 6 amino acid sequence found at positions 79-84 in the HLA-B [α1-domain] sequence, but may include amino acids related to those at HLA-B positions 60-84 [the B2702.60-84 peptide is disclosed in the instant specification], as well as additional irrelevant sequences", that they are CTL immunomodulating compositions and as such must be shown to inhibit CTL-mediated lysis in cytotoxicity assays and/or inhibit anti-CD3-induced proliferation of purified T cells (page 4 at lines 15-24 and page 6 at lines 3-6). The specification does not disclose any peptides comprising the sequences recited in the instant claims wherein the flanking amino acid residues are not from HLA-B positions 60-84, nor wherein the sequences, i.e., the SEQ ID NO or the other disclosed peptides have additions, deletions or modifications, other than to D-amino acid residues or substitutions of specific amino acid residues at specific positions such as those in Table 1 of the instant specification.

An undue amount of experimentation would be involved in determining peptides of undisclosed length and modification that result in those "consisting essentially of" the recited SEQ ID NO from the many possibilities that would be capable of inhibiting CTL-induced cytotoxicity.

Evidentiary reference Nobner et al (J. Exp. Med. 183: 339-348, 1996, Applicant's Exhibit A) teaches that certain amino acid residues at certain positions in the B0701.60-84, B2702.60-84, B0701.75-84 or B27202.75-84 correspond to the "public epitope" Bw4/Bw6 that is thought to be important for CTL inhibitory effects. Nobner et al do not teach peptides that are longer than those of the monomer or of the peptides in Table 1 of the reference, or that have substitutions, additions, deletions or modifications other than a distinct few substitutions at certain positions.

There is insufficient guidance in the specification as to how to make and/or use the instant invention. There is no disclosure in the specification as to which peptide dimers consisting essentially of the SEQ ID NO recited in the instant claims would inhibit CTL-mediated cytotoxicity, except for the peptide dimers consisting of the sequences recited in the instant claims. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 is indefinite in the recitation of "The peptide-like compound of claim 28" because it is not clear what is meant. Base claim 28 recites "A peptide dimer... wherein the dimer consists of" specific fully defined amino acid sequences, i.e., it is a peptide, not a peptide-like compound.

13. Claim 40 is objected to for depending upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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